REMARKS

This Reply is responsive to the Official Action dated October 13, 2000. Entry and reconsideration in light of the amendments and remarks submitted herein is respectfully requested pursuant to 37 CFR §1.112.

First, applicants respectfully note the amendments submitted above. Claims 1, 32, 33 and 35 have been amended in order to delete the word "desired" because it is not necessary to convey the meaning of the claimed methods, i.e., it is clear that the skilled artisan would use the nucleus from a desired cell or cell of interest to perform the method of Claim 1, and generally, it will be a gene of interest to the artisan that is inserted, removed or modified in Claims 32, 33 and 35. Claim 1 was also amended to further clarify the nature of the claimed embryonic or stem-like cells as comprising the nucleus from an adult differentiated cell and the mitochondria from an oocyte of a species other than said adult differentiated cell. Support for this amendment may be found at the very least in the specification at the paragraph bridging pages 13-14, which describes the meaning of the phrase "stem-like cells," and in original Claim 3, which specifies that nuclear donor cells of the present invention may be adult cells. Accordingly, original Claim 3 has been canceled, as has Claim 20 in that it was dependent on Claim 3.

Claim 32 has been amended to clarify at which point in the method of Claim 1 a desired gene is inserted, removed or modified by including an additional step to the claimed method, in order to resolve the antecedent basis issue raised on page 12 of the Office Action. In addition, Claim 31 has been canceled and replaced by new Claim 51 which is dependent on amended Claim 32, in order to provide appropriate antecedent basis for embryonic stem-like cells according to the invention which contain an inserted, removed or modified gene. No new matter has been added through any of these claim amendments.

In addition, new Claim 52 has been added to emphasize that the embryonic or stem like cells of the present invention may be produced whereby the donor adult differentiated cell and the recipient enucleated oocyte are derived from species which are phylogenetically dissimilar. This claim finds support at page 12 of the specification, beginning at line 22, where this novel attribute of the present invention is emphasized. Support may also be found in general throughout the specification, and particularly in Example 1, which describes

nuclear transfer from an adult human differentiated cell into a recipient enucleated bovine oocyte. Therefore, no new matter has been added.

New claims 53-57 have also been added. New Claim 53 presents the method of the invention using language which avoids the phrase "embryonic or stem-like" cells in the event the Examiner is not satisfied with the amendment clarifying the language of Claim 1. Specifically, new Claim 53 is directed to a method of producing an activated nuclear transfer unit capable of being cultured to a size of at least two cells, wherein the nuclear transfer unit comprises mitochondria from a species other than said adult differentiated cell, comprising (i) inserting a human or mammalian cell or cell nucleus from an adult differentiated cell of a first species into an enucleated oocyte of a second species under conditions suitable for formation of a nuclear transfer (NT) unit, and (ii) activating the resultant NT unit so as to produce an activated nuclear transfer unit capable of being cultured to a size of at least two cells. This claim finds support at the very least in original claims 1-3, and in the specification at page 15, lines 7-11. No new matter has been added.

New Claim 54 further specifies that the method of Claim 53 produces an activated nuclear transfer unit capable of being cultured to 2 to 400 cells. Support for this claim may be found in the specification at page 13, line 22 and page 25, lines 19-21. New Claim 55 is dependent on the method of Claim 53, wherein the adult cell inserted into the enucleated animal oocyte is a human cell, and the enucleated oocyte is obtained from an ungulate. Support for this claim may be found at the very least in original claims 2 and 6. New Claim 56 specifies that the ungulate of Claim 55 is a bovine. Support for this claim may be found in original Claim 7, and in Example 1 of the specification. Finally, Claim 57 is directed to the activated nuclear transfer unit obtained according to the method of Claim 53. No new matter has been added.

Turning now to the Office Action, Claims 1-25 and 31-50 were provisionally rejected under 35 U.S.C. §101 for allegedly claiming the same invention as that claimed in Application No. 08/699,040 and Application No. 09/032,945. Because this is a provisional rejection and the claims may be amended through the course of prosecution, Applicants respectfully request that this rejection be held in abeyance until allowance is negotiated. At that time, if the claims in the instant application and those of the related application are still

deemed to be obvious over eachother, Applicants will consider submitting a terminal disclaimer.

Claims 18-23 were rejected under 35 U.S.C. §101 for allegedly claiming non-statutory subject matter. It is the Examiner's opinion that the claims as written read on cells that are a human embryo. Applicants respectfully submit that this rejection should be resolved by the amendments submitted above and the remarks herein, which clarify the meaning of an "embryonic or stem like cell" according to the invention. Furthermore, the claims have been amended to now refer to an embryonic stem-like cell to further clarify the phrase is not intended to encompass an actual embryo. Withdrawal of the rejection is respectfully requested.

Claims 1-25 and 31-50 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Essentially, it is the Examiner's opinion that, although Example 1 of the specification is acknowledged to result in the production of a nuclear transfer unit (16-400 cell stage) that appears to be ES-like, Applicants have allegedly failed to demonstrate that the ES-like cells are totipotent or that they function as stem cells capable of differentiating into other multilineage cell types. The Examiner therefore concludes that Applicants have failed to enable the production of embryonic or stem-like cells as recited in step (iv) of Claim 1. The Examiner further alleges that, because it is unclear whether the resultant ES-like cells differentiate into other cell types useful for transplantation, it is unknown how the skilled artisan would be able "to use" the claimed embryonic or stem-like cells in a manner which is consistent with the specification (page 6 of the Official Action).

The Examiner also raises the point that it is allegedly inappropriate to rely on the prior art with respect to any other species with regard to ES cell differentiation techniques because results are species dependent, and one would not reasonably expect the to induce cell differentiation in other cell lineages using techniques available for mouse ES cells (pages 6-7 of the Office Action). The Examiner also questions the contribution of the oocyte cytoplasm or mitochondria in the cross-species ES-like cells of the invention, and relies on a reference by Dominko et al. as suggesting that the success of cross-species nuclear transfer cannot be

judged until somatic cell/recipient cytoplasm compatibilities are examined (pages 7-8). The Examiner makes specific opposition to the terminology "embryonic or stem-like cells" to the extent that it reads on common embryonic stem cells (page 9). In this regard, the Examiner notes that true human ES cells have the potential to develop into a human being, and suggests that Applicants choose different claim terminology if this is not an intended use of the cells (page 9).

Finally, with regard to claims 31-42, the Examiner notes that the specification fails to teach gene modification of any differentiated cell, and fails to teach the use of gene-modified cells as a starting point for nuclear transfer (page 10). Applicants respectfully traverse all these grounds for the rejection, and request reconsideration with regard to each claim taken individually in light of the following remarks and the amendments entered above.

First, Applicants again note the amendments submitted above. Because it appears that one of the Examiner's main concerns is the terminology "embryonic or stem-like cells," Applicants have clarified this phrase in the preamble of Claim 1 by emphasizing that such cells comprise a nucleus derived from an adult differentiated cell and mitochondria from an oocyte of a species other than said adult differentiated cell. Thus, the cells produced by the claimed method are different from embryonic stem cells as they are commonly known in the art, in that the cells contain nuclear DNA and mitochondrial DNA respectively derived from different species.

The fact that nuclear transfer derived embryonic stem cells and the differentiated cells, tissues and animals derived therefrom retain the mitochondria from the enucleated recipient cell has been verified by several post-filing date references. For instance, Takeda et al. (1999) report "dominant distribution of mitochondrial DNA from recipient oocytes in bovine embryos and offspring after nuclear transfer" (see title and abstract). Evans et al. (1999) report that the mitochondrial DNA in the cloned sheep Dolly, as well as that in nine other nuclear transfer-derived sheep, was derived exclusively from recipient enucleated oocytes with no detectable contribution from respective somatic donor cells. These reports are consistent with observations gleaned from sexual mammalian fertilization, whereby the mitochondria derived from sperm are reportedly eliminated during early embryogenesis (see Kaneda et al., 1995; references are attached). Thus, the ES-like cells derived from the

present invention are clearly different than classical embryonic stem cells, in that the nuclear and mitochondrial DNAs are cross-species with regard to one another.

Nevertheless, the fact that the ES-like cells of the present invention contain xenogeneic mitochondria does not mean that such cells are not capable of differentiating into other cell types, or even differentiating into a mammal (although this is not the intent for the human ES-like cells of the present invention). That such cross-species differentiation and development is possible is evidenced by recent data gathered by the present inventors which shows that it is possible to use nuclear transfer from a somatic cell from a gaur into an enucleated oocyte of a bovine to produce a cloned gaur having bovine mitochondria. A copy of a recent publication detailing these results is attached for the Examiner's review, and Applicants would be amenable to submitting this data in the form of a declaration if the Examiner indicates that this would be helpful.

While the production of the cloned gaur is evidence that cross-species nuclear transfer may be used to produce embryonic or stem-like cells which differentiate and develop into a mammal, Applicants again emphasize that their intention in using human cells as nuclear transfer donors is not to produce adult cloned humans. Rather, cross-species nuclear transfer can be valuable in the production of human ES-like cells that may be used to produce differentiated cells and tissues for the purpose of transplantation. While Applicants acknowledge that the instant specification does not disclose the actual production of human differentiated tissues, it is entirely reasonable to expect that such results are readily achievable given the production of a cloned gaur using cross-species transplantation, and the novel showing by Applicants that human cross-species nuclear transfer into a bovine generates a unit with ES cell-like morphology. It also follows that such tissues would be ideally suited for transplantation and cell therapies given that the tissues may be designed using a cell or nucleus from the patient in need of such transplantation or therapy.

Applicants acknowledge that the cross-species human nuclear transfer described in Example 1 differs from the gaur report in that the bovine is more phylogenetically related to the gaur than it is to the human. However, it would be certainly possible to perform the cross-species nuclear transfer of the present invention using a recipient oocyte or other suitable cell from a species more evolutionarily related to the human. For instance,

Applicants have recently demonstrated the production of primate embryonic stem cells using embryos produced from parthenogenetic primate embryos (produced by in vitro activation of cynomolgous monkey oocytes) wherein blastocysts, when cultured on a feeder layer, gave rise to differentiated cell types. This substantiates Applicants' argument that it is reasonable to assume that a primate (human) blastocyst, containing DNA of human origin, will give rise to differentiated cells or tissues when cultured under appropriate conditions. Indeed, given that several different types of mammals have now been cloned, and given Applicants' recent success in producing primate embryonic stem cells, and further given the success in cross-species nuclear transfer in the production of a cloned gaur, it is entirely reasonable to expect that cross-species nuclear transfer of a human donor cell could be accomplished using at the very least a phylogenetically related recipient oocyte according to the present invention. A copy of Applicants' results pertaining to the production of primate ES cells is attached for the Examiner's review, and Applicants would be amenable to submitting this data in the form of a declaration if the Examiner indicates that this would be helpful.

The Examiner seems to take particular opposition to the phrase embryonic or stem-like cells with regard to the production of differentiated cells and cloned mammals as it pertains to the use of human donor cells. While Applicants understand the Examiner's concern that such cells could have the potential to be used to create a cloned human, the same could be said for other patented cells and cell lines (see, e.g., U.S. Patent 6,200,806 of Thomson, and specifically, claim 9, directed to a pluripotent human embryonic stem cell line). Applicants cannot see where calling the cells something different somehow negates this potential. Applicants have emphasized above that the cloning of humans is not intended by the present invention, and have expressly disclosed that human cross-species nuclear transfer is useful for the generation of transplantation cells and tissues, and this should be sufficient. Nevertheless, Applicants have included new claims 53-57 directed to methods of making nuclear transfer units according to the invention in case the Examiner still dislikes the original terminology.

Furthermore, the generation of differentiated cells for transplantation is not the only utility for the nuclear transfer units generated by the claimed methods. For instance, on page 1 of the specification, Applicants note that embryonic stem cells provide an *in vitro* model for

differentiation, and as such can be used in the study of genes which are involved in the regulation of early development. Human cross-species ES-like cells in particular can be used to identify important human regulatory genes, and would be highly useful in this regard even if they were not used for transplantation purposes. Indeed, the fact that Applicants have found that cross-species nuclear transfer of a human cell into a bovine cell generates an activated nuclear transfer unit capable of division is an enormously exciting and important finding. For example, such cells provide a model for deciphering the role of the mitochondrial genome in mammalian development and cellular function.

Thus, Applicants believe that the activated cross-species nuclear transfer units claimed in Claim 53 are fully enabled by the specification, and moreover have significant utility even if they are not used to produce differentiated cells and tissues for transplantation. However, Applicants respectfully emphasize that this does not mean that such activated nuclear transfer units could not be used to produce embryonic stem-like cells capable of being used for this purpose. Rather, Applicants believe the gaur data attached hereto demonstrates that cross-species nuclear transfer may be used to generate differentiated cells and tissues and even adult mammals. Furthermore, Applicants' success in producing primate stem cells demonstrates that there is no species barrier with regard to producing ES-like cells from activated oocytes that express primate DNA. Taken together with the gaur cross-species data, the primate stem cell data also suggests that cloned human differentiated cells may be produced using the methods disclosed in the specification using a phylogenetically similar recipient cell.

Finally, with regard to gene-modified differentiated cells, such cells have been commonly produced in the art for some time so it cannot be argued that it would require undue experimentation to transfect a differentiated cell with a gene of interest. Indeed, the present invention provides an advantage over previous nuclear transfer methods, which typically employed embryonic cells which are more difficult to carry in culture and hence more difficult to modify with a gene knock-in or knock-out. Yet, researchers have been genetically modifying ES cells for years. Thus, there is no reason to believe that the differentiated donor cells used in the present invention could not be genetically modified as described in the present disclosure in order to affect the claimed methods. Furthermore, there

would be no reason to believe absent some evidence to the contrary that a donor cell containing a heterologous gene could not just as readily be used as a donor cell for nuclear transfer as described in the present disclosure.

In view of all the remarks and evidence submitted above, Applicants respectfully reconsideration and withdrawal of the rejection of Claims 1-25 and 31-50 under 35 U.S.C. §112, first paragraph. Furthermore, Applicants respectfully request individual consideration of the newly submitted claims in light of the above remarks, and request that the rejection under §112, first paragraph not be extended to Claims 51-57.

Claims 1-25 and 31-50 were also rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Specifically, Claims 1, 15, 16, 18-23, 32 and 34 were rejected because it was not clear what was intended by the phrase "embryonic or stem-like cells." Applicants respectfully submit that the amendment to the preamble of Claim 1 submitted above sufficiently clarifies what was intended by this terminology, and furthermore that the word "or" has been deleted from the phrase to avoid any confusion with an embryo. Therefore, the rejection has been rendered moot. Withdrawal of the rejection is respectfully requested.

Claims 1, 32, 33 and 35 were rejected because the word "desired" is allegedly vague and indefinite. Applicants disagree that the meaning of this term is unclear, and believe rather that it adequately reflects that the intention of the claimed method may vary depending on the artisan who practices the claimed invention. Nevertheless, the word has been deleted in the rejected claims by way of amendment above, and withdrawal of this rejection is respectfully requested.

Claim 31 was rejected because there was allegedly insufficient antecedent basis for the limitation "which contain and express and inserted gene." Claim 31 was canceled and replaced by new Claim 51, which depends on Claim 32 instead of Claim 1. Because Claim 32 introduces a step whereby a gene is inserted, removed or modified, it appears to provide sufficient antecedent basis for new Claim 51. Withdrawal of this rejection is respectfully requested.

Claim 32 was rejected because the phrase "wherein a desired gene is inserted, removed or modified," allegedly has no antecedent basis in Claim 1. Claim 32 has been

amended to rephrase the limitation in the form of an additional step, therefore, this rejection has been rendered moot. Withdrawal is respectfully requested.

Claim 46 was rejected because it is allegedly unclear whether the claim is drawn to a fusion protein or whether the cyclin is a promoter that controls expression of a detectable marker. Applicants believe that the claim is clear when read in light of the specification at page 33, lines 9-10, which discloses that a cyclin gene may be operably linked to a regulatory promoter along with a detectable marker gene. Thus, the claim would cover the situation where expression of both a cyclin gene and a detectable marker are linked to a regulatory promoter, either independently, or via fusion (i.e., note the and/or terminology).

Next, Claim 18 was rejected under 35 U.S.C. §102(b) as being anticipated by Bradley et al. It is the Examiner's opinion that, because Bradley et al. teaches mouse embryonic stem cell lines, and the product embryonic or stem-like cell claimed in Claim 18 is not distinguished by its method of manufacture, Bradley allegedly anticipates the claimed cells. Applicants respectfully submit that the amendment to Claim 1 clearly shows that the embryonic or stem-like cells of the present invention may be distinguished by classical embryonic stem cells of the prior art in that the mitochondria of the claimed cells are derived from the recipient oocyte (with reference to the comments submitted in response to the §112, first rejection above). Therefore, the mouse ES cells of Bradley do not anticipate those of the claimed invention, and the rejection should therefore be withdrawn.

Likewise, Claims 18-25 were rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Tsukamoto et al. Again, because the Examiner was of the opinion that the phrase "embryonic or stem-like cells" encompassed the embryonic stem cells of the prior art, the human embryonic stem cells of Tsukamoto were alleged to anticipate the embryonic or stem-like cells of the present invention. However, Applicants respectfully submit that it is now clear that the embryonic or stem-like cells of the present invention contain xenogeneic mitochondria in view of the amendments presented above. Moreover, no prior art reference describes such cells, including Tsukamoto. Withdrawal of the rejection in view of the above amendments is respectfully requested.

Likewise, Claims 18-23 were rejected under 35 U.S.C. §102(a) as being allegedly anticipated by Granerus et al. Again, because the Examiner was of the opinion that the

phrase "embryonic or stem-like cells" encompassed the embryonic stem cells of the prior art, the human embryonic stem-like cell line, Tera 2, of Granerus was alleged to anticipate the embryonic or stem-like cells of the present invention. However, Applicants respectfully submit that it is now clear that the embryonic or stem-like cells of the present invention contain xenogeneic mitochondria in view of the amendments presented above. Moreover, no prior art reference describes such cells, including Granerus. Withdrawal of the rejection in view of the above amendments is respectfully requested.

Likewise, Claims 18-25 were rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Yamane et al. Again, because the Examiner was of the opinion that the phrase "embryonic or stem-like cells" encompass the stem cells of the prior art, the human epithelial and endothelial stem cells of Yamane were alleged to anticipate the embryonic or stem-like cells of the present invention. However, Applicants respectfully submit that it is now clear that the embryonic or stem-like cells of the present invention contain xenogeneic mitochondria in view of the amendments presented above. Moreover, no prior art reference describes such cells, including Yamane. Withdrawal of the rejection in view of the above amendments is respectfully requested.

Claim 31 was rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Tsukamoto. Note that Claim 31 has been canceled in favor of new Claim 51 to provide antecedent basis for the inserted gene. Nevertheless, it is the Examiner's opinion that it would have been obvious to modify differentiated human cells produced from stem cells as described by Tsukamoto to arrive at the genetically modified cells as claimed in Claim 31. However, the embryonic stem cells of Tsukamoto cannot reasonably be interpreted as anticipating or rendering obvious the embryonic or stem-like cells of the present invention because the cells described in the present invention have xenogeneic mitochondria. Therefore, withdrawal of this rejection is respectfully requested.

Finally, Clams 1-25 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Wolfe et al. taken with Collas et al. Essentially, it is the Examiner's opinion that, although Wolfe et al. fails to teach cross-species nuclear transfer of human or mammalian differentiated nuclei (teaching only cross-species nuclear transfer using bovine nuclei from embryos), it would have been obvious to use differentiated cells in view of the

teaching in Collas et al. that a variety of differentiated mammalian cell types might be used for nuclear transfer. Applicants respectfully traverse, however, on the basis that Collas et al. makes no mention that such differentiated cells might be used in cross-species nuclear transfer. It would not have been reasonable to expect at the time the present invention was made that an adult differentiated somatic cell could be reprogrammed by an enucleated oocyte of an entirely different species, let alone a species as evolutionarily diverse as a bovine is to a human nuclear donor.

Furthermore, it would not have been reasonable to expect based on the combined teachings of Wolfe et al. and Collas et al. that cross-species nuclear transfer using an adult differentiated cell could be used to generate embryonic-like stem cells that could then be used to produce differentiated cells, tissues for transplantation, and even live mammals. Indeed, as the Examiner even acknowledges by reference to Dominko et al. (page 7 of the Office Action), successful reprogramming is only satisfactorily proven when one can show a pregnancy carried to term. With the eminent birth of the cloned gaur using cross-species nuclear transfer, and the detailed characterization of the fetal development of the cloned gaur, Applicants are the first to actually demonstrate that cross-species nuclear transfer can be used to generate cloned tissues and mammals from an adult differentiated cell, wherein such mammals are shown to have mitochondria derived from the original recipient oocyte.

The Federal Circuit has recognized that one way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results," i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward- that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results. In re Soni, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995).

By the Examiner's own discussion in the enablement rejection, and given the statements in Dominko et al concerning the lack of predictability expected in producing cross-species nuclear transfer derived differentiated cells and tissues, one of ordinary skill in

the art would not have expected at the time the invention the present invention was made that cross-species nuclear transfer could be used to generate fully developed mammals. The results achieved with the cross-species cloned gaur would therefore have been highly unexpected, and certainly would not have been obvious in view of the combined disclosures of Wolfe et al and Collas et al. Indeed, Collas et al. does not even concern cross-species nuclear transfer.

In view of the fact that Wolfe et al. fails to teach cross-species nuclear transfer from an adult differentiated cell, and given that the teachings in Collas et al. regarding the use of differentiated cells can only reasonably be applied to same-species nuclear transfer, reconsideration and withdrawal of the rejection under §103(a) based on Wolfe and Collas is respectfully requested.

This Reply is believed to be fully responsive to the Office Action dated October 13, 2000. Accordingly, a Notice of Allowance appears to be next in order. The undersigned welcomes any questions or suggestions the Examiner might have regarding the Reply or application in general, and would be earnestly amenable to resolving any further outstanding issues by telephone conference such that allowable claims might issue from the present application.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: _____
Bonnie Weiss
Registration No. 43,255

1100 New York Ave. NW
Ninth Floor, East Tower
Washington, D.C. 20005-3918
(202) 861-3000
(202) 822-0944 Facsimile

Date: April 11, 2001

APPENDIX: VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 3, 20 and 31 are cancelled.

The claims are amended as follows:

1. (Amended) A method of producing embryonic or stem-like cells, wherein said cells comprise a nucleus derived from an adult differentiated cell and mitochondria from an oocyte of a species other than said adult differentiated cell, comprising the following steps:

(i) inserting a [desired] differentiated human or mammalian cell or cell nucleus into an enucleated animal oocyte, wherein such oocyte is derived from a different animal species than the human or mammalian cell under conditions suitable for the formation of a nuclear transfer (NT) unit;

(ii) activating the resultant nuclear transfer unit;

(iii) culturing said activated nuclear transfer units until greater than the 2-cell developmental stage; and

(iv) culturing cells obtained from said cultured NT units to obtain embryonic [or] stem-like cells.

15. (Amended) The method of Claim 1, wherein the resultant embryonic [or] stem-like cells are induced to differentiate.

16. (Amended) The method of Claim 2, wherein the resultant embryonic [or] stem-like cells are induced to differentiate.

18. (Amended) Embryonic [or] stem-like cells according to the method of Claim 1.

19. (Amended) Human embryonic [or] stem-like cells according to the method of Claim 2.

21. (Amended) Human embryonic [or] stem-like cells according to the method of Claim 4.

22. (Amended) Human embryonic [or] stem-like cells according to the method of Claim 6.

23. (Amended) Human embryonic [or] stem-like cells according to the method of Claim 7.

32. (Amended) The method of Claim 1, [wherein] further comprising a step (v) whereby a [desired] gene is inserted, removed or modified in said embryonic [or] stem-like cells.

33. (Amended) The method of Claim 32, wherein [the desired] said gene encodes a therapeutic enzyme, a growth factor or a cytokine.

35. (Amended) The method of Claim 32, wherein [the desired] said gene is removed, modified or deleted by homologous recombination.